Organization: Duke University Medical Center

Title: Development of Combined Computational and Experimental Approaches for Using Molecular Engineering in the Design, Construction and Analysis of Integrated Biosensor Microsystems

MTO **Simbiosys**

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Project Goals

The Goal of this project is the development and experimental validation of computational methods for the design of protein-based biosensors that selectively bind to a wide variety of small molecules, proteins and nucleic acids.

Technical Approach

- We develop molecular design software that predicts the mutations needed to construct a stereochemically complementary surface for a ligand docked into the binding pocket of a protein of known structure. These algorithms are then tested by constructing the predictions in the laboratory using molecular cloning techniques to build and produce mutant proteins, the binding properties of which are then analyzed using appropriate biophysical techniques.

Recent Accomplishments

- Development of first-generation software that designs receptor surfaces for small ligands.
- Experimental demonstration of computationally designed TNT sensors
- Development of software for a) generating scaffold structure diversity, b) design of receptors for moderately flexible ligands.

Six-Month Milestones

- Design of receptors for molecules that are relatively rigid with few internal degrees of freedom (less than six). Organophosphates will be used as experimental test cases for this method.
- Development of methods to deal with ligands that are very flexible. Oligosaccharides will be used as experimental test cases.
- Development of methods for the design of protein/protein interactions
- Development of methods for the design of heterologous macromolecular assemblies. We will focus on protein/DNA interactions

Team Member Organizations

Department of Biochemistry, Duke University Medical Center